THYROTROPIC EXOPHTHALMOS*

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THE demonstration of the production of exophthalmos by an anterior pituitary principle in animals, has served to explain several aspects and the extremely variable clinical appearance and course of this ocular disorder in man, when associated with thyroid dysfunction. The experimental studies of Smelser,[1-3] Pochin,[4] and Marine and Rosen,[5] indicated the existence of a different type of exophthalmos of Graves' disease with quite a different significance, viz., thyrotropic exophthalmos, as distinguished from thyrotoxic exophthalmos or that commonly associated with hyperthyroidism. Though the linkage may be incomplete, this newly separated type seems to correspond clinically precisely with those cases which showed after operation a progression, if not a malignant increase, in exophthalmos. With a different pathogenesis, diverse pathologic changes, and running a dissimilar course, this type requires different treatment, for indeed the choice of wrong therapeutic measures may lead to most unfortunate consequences.

The discovery of the thyrotropic hormone of the pituitary *marked* the beginning of our understanding of the interaction of the thyroid and the pituitary, on the production of a diversity of ocular complications, the most striking of which is exophthalmos. In his experiments, Smelser[1] showed that extracts of the anterior pituitary produce an extreme, forward displacement of the eyes in thyroidectomized guinea pigs, and that the exophthalmos persisted unchanged after death. In thyroidectomized animals which had the cervical sympathetic ganglion on one side removed in addition, injected extracts of ox anterior lobe pituitrin produced the proptosis of equal extent on both sides Thus, in this experiment, he eliminated the role of sympathetic stimulation as a cause of the displacement of the eyes. The effects of excess thyroxin or epinephrin in guinea pigs are entirely different.

In contradistinction to the exophthalmos of thyrotoxic goitre which

* Read at The Stated Meeting of The New York Academy of Medicine March 2, 1950.

is due mainly to sympathetic stimulation of muscle by adrenalin, when sensitized by an excess of thyroxin in the blood, a type of displacement which disappears on death, the *exophthalmos* of thyrotropic origin is real, viz., it is due to an increase in orbital content. A change in water balance produces edema of the tissues of the orbit, conjunctiva and lids. Round cell infiltration of muscles and lacrymal gland, and connective tissue hyperplasia and edema of the fat of the orbit occurs. Smelser estimated the constituents of the orbital contents of his animals to have increased 100 per cent in fat, 40 per cent in the dorsal lacrymal gland and 22 per cent in the extrinsic muscles. He found this connective tissue hyperplasia to have occurred also in other parts of the body where the fat is rich in connective tissue. Curtis[6] called attention to the fact that localized myxedema may follow surgical removal of a thyrotoxic gland. These histologic changes with rather more hypertrophy and fragmentation of the muscles, with late secondary fibrosis in long standing cases, have been confirmed in large part on human tissue.

The ocular and general signs of thyroid dysfunction depend upon the preponderance of action of the thyroid, or of the pituitary gland. Excess thyroxin with a minimum of anterior pituitrin produces the classic picture of hyperthyroidism with which every one is familiar.[7-9] The clinical appearance of a patient with excess anterior pituitrin (or thyroid-stimulating hormone) and with little, or an absence of thyroxin, may merit description. In these cases the basal metabolism may be very slightly raised, or normal, but is usually subnormal. Sympatheticotonia is absent. The eye signs are extreme and characteristic. In its pure form this entity is relatively uncommon and, as should be expected, mixed types are more frequent, viz., those which show some accompanying thyrotoxicity. Clinically one encounters the more frequent pure thyrotoxicosis on one hand, and, ranging through cases of diminishing thyrotoxicosis and increasing thyrotropism, cases of the less common, pure, thyrotropic variety on the other hand.

The eye signs offer the earliest and easiest means of differentiating these groups and it is these changes which frequently compel the patient to seek medical attention.[10]

The classic ocular and general signs of diffuse toxic goitre are well known. The widening of the interpalpebral fissure, the retraction and lagging of the upper eyelid and the infrequency of winking produce the staring expression and create the appearance of exophthalmos, which

may not be present in fact. The excursions of the eyes are not interfered with and exophthalmos, if present, is reducible on pressure. These eye findings are relieved, at least in part, by adequate reduction of the activity of the thyroid gland.

In thyrotropic exophthalmos the displacement of the eye appears early in the disease, is frequently unilateral, so that an orbital tumor is suspected, and is progressive.[11] Tearing, with edema of the eyelids and conjunctiva may appear early and may be severe. Redundancy of the bulbar conjunctiva with folds overlying the lower lids, or even prolapse, is common and suggestive. The excursions of the eyes are limited in all directions of gaze due to the histologic changes affecting all of the muscles of the affected eyes, causing the patient to complain of diplopia; thus, the name exophthalmic ophthalmoplegia is sometimes applied to this disorder. In the severe or malignant form, which may develop with amazing rapidity, especially after thyroidectomy, the eyes become extremely proptosed, solidly fixed in position, chemotic and with lids edematous and unable to cover the eyes. Exposure keratitis then develops, ulceration follows and loss of the eyes results. Treatment, therefore, must be prompt and effective.

In an effort to clarify the roles played by the thyroid and pituitary glands respectively in individual patients, excluding the pure thyrotoxic cases, Mann[12] classified her cases in three groups as follows:

Group 1: Primary deficiency of thyroxin with compensatory excess of thyrotropic hormone secretion. These cases showed the thyrotropic exophthalmos without thyrotoxic eye and general signs, and with thick coarse skin, rather suggesting myxedema.

Group 2: Primary excess thyroxin as initial symptom, followed by thyroid atrophy or removal, replaced by excess thyrotropic hormone. In these cases the initial symptoms were those characteristic of thyrotoxicosis, while the later signs were those produced by excess thyrotropic hormone. This is the type of case which every physician has seen following thyroidectomy, in which the exophthalmos increased to an alarming degree, frequently ending in loss of the eyes. The increase may follow the operation by a few weeks or it may require several years. Since malignant exophthalmos occurs disproportionately more frequently in men, in whom thyroid dysfunction is much less frequent than in women (1 case to 10), all cases in men should be carefully searched for evidence of the thyrotropic element.

It is this group that is of greatest interest to the surgeon, for he must be able to determine whether or not this most unfortunate complication will follow the treatment or removal of the thyroid gland. It may not be possible to predict in every case with assurance what might be expected to follow the operation. Sloan[13] has emphasized certain significant findings with which every physician, and certainly every surgeon, engaged in the treatment of thyroid dysfunction should be familiar.

Group 3: Excess thyroxin and excess thyrotropic hormone arising simultaneously. In this group of cases one observes both specific and infiltrative changes in the orbits. The classic eye signs of thyrotoxicosis may be observed in addition to edema of the eyelids and conjunctiva, solid proptosis, and impairment of motility of the eyeballs. The proper management of this group is as yet to be found. Thyroidectomy is prone to lead to malignant exophthalmos and must be avoided. Attention should be directed more toward suppressing the thyrotropic element rather than the thyrotoxic.

Treatment

The treatment of exophthalmos associated with thyroid dysfunction must be directed toward the underlying cause, the general manifestations of the disease and the management of the ocular complications. Our province in this presentation is especially concerned with the management of the ocular complications and the preservation of vision. Close coöperation between the surgeon, internist and ophthalmologist is called for and treatment of the eyes should be concerned more with prevention than with cure.

It is imperative that every surgeon be familiar with the ocular manifestations of thyroid disease. Not only because they indicate the proper course of treatment but also because blindness is a very real threat. In his interest in the preservation of sight, the ophthalmologist, in addition to the treatment carried out by the internist, may employ several local measures. The protection of the eye from exposure which leads to ulceration is his foremost consideration. The placing of intermarginal lid adhesions serves this end best but these must be placed before the tension of the eye and eyelids is too great. Such adhesions may be left as long as desired and severed at any time. Excision of the edematous conjunctiva, or removal of the tissue from the lids is not helpful. In extreme cases where intermarginal adhesions cannot be placed, orbital decompression

has to be resorted to. Naffziger's[14] intercranial method of removing the roofs of the orbits may be helpful. Other surgeons have advocated removal of the lateral walls of the orbits or depression of the floors into the antra. With proper medical care and prompt insertion of intermarginal adhesions this radical surgery may be avoided. The correction of diplopia, which may be the patient's leading ocular complaint may be extremely difficult, if not impossible. Surgical measures on the extraocular muscles themselves offer the best chance but this should be delayed until all signs of general activity have subsided. Spontaneous regression of the ocular complications may occur after some months or years and temporizing measures to preserve the eyes may be justified.

SUMMARY

Sloan[13] has emphasized conservatism in cases manifesting thyrotropic disturbance. He especially mentioned cases showing exophthalmos out of proportion to the degree of hyperthyroidism as a bad prognostic sign. Asymmetric exophthalmos is frequently due to infiltrative changes and will increase after thyroidectomy. Diplopia, or ocular muscle paralyses indicate infiltrative orbital changes and should serve as a warning to the surgeon. The absence of a high basal metabolic rate should alert the physician to the predominance of the thyrotropic element. The overactivity of this anterior pituitary hormone is held in check by the excess of thyroxin. Reducing the thyroxin supply by operation or medical treatment may allow the thyrotropic hormone to run amuck to produce the distressing conditions known as malignant exophthalmos or exophthalmic ophthalmoplegia. Let the surgeon, therefore, beware of operating upon any patient showing these signs and if they should arise following operation, it is necessary to raise the metabolic rate to stop the progress of the disease. At the same time measures must be taken to safeguard vision.

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